

PATENT SPECIFICATION

NO DRAWINGS

837,465



Date of Application and filing Complete

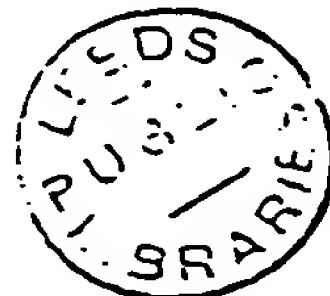
Specification: Jan. 27, 1958. No 1,441,58.

Application made in United States of America on Jan. 31, 1957.

Application made in United States of America on Aug. 23, 1957.

Application made in United States of America on Jan. 3, 1958.

Complete Specification Published: June 15, 1960.



Index at acceptance :—Classes 81(1), B(3:7); and 102(2), B3(A3D:B12).

International Classification :—A61k. B65d.

COMPLETE SPECIFICATION

Self-propelling, Powder-dispensing Compositions

We, RIKER LABORATORIES, INC., a Corporation organised under the Laws of the State of Delaware, United States of America, of 8480 Beverly Boulevard, Los Angeles 48, California, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to self-propelling, powder-dispensing compositions capable of dispensing powdered material in aerosol form and to a means for dispensing a dry powder in aerosol form having controlled particle size.

Previously it has not been possible to provide stable suspensions of powder of substantially uniform particle size in a liquefied propellant for use in a pressurized container for aerosol dispensing which would not cause the closure valve, and particularly a metering valve, to stick. It has generally been the practice to prepare self-propelling compositions for aerosol administration by rendering the solid, active ingredient soluble in the liquefied propellant by means of a cosolvent. Usually the cosolvent is polar in character, e.g., alcohol. Unfortunately, many solids, and particularly certain medicaments, are not stable in polar solvents such as water, or they are rendered unstable when in a polar solvent and in contact with the metal of which the valve of a pressure-tight container is usually constructed. This is the case with epinephrine. These polar solvent-containing systems may also attack and corrode the metal valve closures of the containers and interfere with their functioning. Also, some medicaments and other solids cannot be satisfactorily solubilized in the usual liquefied propellants, even though a cosolvent is employed. By means of the

present invention it is possible to overcome these shortcomings of the prior art and to provide simple, more stable and more satisfactory aerosol-producing compositions.

It is an object of this invention to provide a package from which a dry powder may be dispensed as an aerosol in a stream of moving gas in a controlled manner or in metered quantities.

It is a further object of the present invention to provide stable suspension compositions of powdered solids which may be dispensed effectively and efficiently in aerosol form in measured quantities, wherein the compositions remain substantially homogeneous and attractive in appearance during storage.

It is another object to provide stable therapeutic compositions which are self-propelling and which may be dispensed consistently in accurate doses through a metering valve for inhalation therapy without causing toxic or irritating side effects on the user.

It is an additional object of the present invention to provide stable self-propelling suspension compositions of powdered solids with reduced tendency to deposit on the container walls above the liquid level or "cake out".

It is also an object to provide a method for efficiently and effectively dispensing a dry powder in aerosol form of controlled particle size in a manner which avoids sedimentation and particle agglomeration or interference with the functioning of the valve closure and metering mechanisms.

In accordance with the invention, there is provided a self-propelling composition capable of dispensing a powder in aerosol form and comprising a finely divided powder suspended in a mixture of a liquefied propellant having a boiling point below 65°F. at atmospheric pressure and

[Price 3/6]

a liquid, non-ionic surface-active agent.

The finely divided powder may constitute from 0.01 to 20% by weight of the total composition. Desirably it shall 5 constitute from 0.05% to 10%, and preferably 0.1 to 3% by weight of the total composition. The surface-active agent may constitute from 0.1 to 20%, desirably between 0.25 and 5%, and preferably, for 10 medicinal purposes, between 0.25 and 1%, by weight of the total composition, with the liquefied propellant constituting the remainder of the composition. For best 15 results, the concentration of surface-active agent is kept at a minimum as it may tend to solubilize the powder in the propellant, which is undesirable for reasons which will be explained below.

We have discovered that considerable 20 deviation is permissible if the particle size of the powder is small enough. For pharmaceutical purposes the particle size of the powder should desirably be uniform and not greater than 100 microns diameter. 25 since larger particles may tend to agglomerate, separate from the suspension and may clog the valve or orifice of the container. Preferably the particle size should be less than 25 microns in diameter. 30 Desirably the particle size of the finely-divided solid powder should for physiological reasons be less than 25 microns and preferably less than 10 microns in diameter. For best results, the size of the 35 particles of powder should be substantially uniform. There is no lower limit of particle size except that which is imposed by the use to which the aerosol produced is to be put. Where the powder is a solid 40 medicament, the lower limit of particle size is that which will be readily absorbed and retained on or in body tissues. When particles less than one micron per diameter are administered by inhalation they tend to 45 be re-exhaled by the patient.

Desirably the finely-divided powder should be substantially insoluble in each of the liquefied propellant, the surface-active agent and in the liquefied propellant- 50 surface-active agent mixture. In the majority of cases we find that solid compounds which are predominantly polar in nature by reason of a sufficient number of polar substituent groups such as hydroxyl, 55 amino and carboxyl groups, and salts thereof, provide most satisfactory compositions in accordance with the invention. If the powder is substantially soluble, crystal growth may occur and the particle size of 60 the aerosolized powder when dispensed cannot be controlled. Since the compositions of the invention are intended to be used for dispensing powders in aerosol form by operating the valve of a pressure- 65 tight container charged with the composi-

tions, it is desirable that the particle size of the suspended powder be regulated and agglomeration reduced. It is clear that if agglomeration of the powder takes place, it may tend to clog the narrow valve orifice 70 and render the dispensing device inoperative, or if a metering valve is employed, it may be rendered inaccurate. This may lead to inaccurate dosages, which in the case of highly potent medicinals may lead 75 to undesirable results. In addition to increasing the particle size and clogging orifices, agglomeration may make the suspension unstable and of unsuitable appearance. In the case of powdered 80 medicinals, adsorption in the body may be made ineffective. Consequently, it is desirable that the finely-divided powder be substantially insoluble in the other components of the compositions. 85

Where a finely-divided powder, such as a medicament, tends to be somewhat soluble in the mixture of surface-active agent and liquefied propellant, it is sometimes possible to overcome this difficulty by employing a 90 less soluble form of the powder. For example, instead of employing the base phenylephrine, its hydrochloride may be employed. Also, different liquefied propellants may be employed in which the 95 powder is less soluble.

Illustrative of the versatility of the compositions of the invention is the fact that the solid components may be amorphous or crystalline in nature. We prefer to use 100 crystalline materials, as is indicated by the specific examples given below. Early efforts to produce self-propelling powder dispensing compositions showed that even to obtain compositions having only borderline properties, it was necessary to limit the solid materials employed to amorphous materials.

As will be apparent to those skilled in the art, one of the advantages of the compositions of the present invention is that they do not require the presence of a polar solvent, such as water. The compositions may be substantially anhydrous.

In carrying out the present invention, especially where water-soluble medicaments are employed, we have discovered that moisture control is important at all stages of processing. We have found that the total moisture content for finely-dispersed water-soluble medicaments should be less than 300 parts per million by weight of total composition. This moisture control has been found to be critical to ensure the stability of the suspension during periods of storage. For instance, in the case of Example 10 hereinbelow, when more than 300 parts per million of water are present, the medicament agglomerates within one month at 130

room temperature and deposits on the walls of the container. This adversely affects the dose delivered, in addition to resulting in a pharmaceutically inelegant preparation.

5 Another means of controlling and reducing the moisture content of the composition is to introduce before closing the container in which the composition is packaged, small fragments of an anhydrous, non-reactive desiccant, such as silica gel or calcium sulfate. This reduces the moisture content of the liquid phase of the composition below that which causes agglomeration. Usually 100 mgm. of desiccant is sufficient 10 for a 10 ml. container charged with composition.

The solid active component to be aerosolized may be a medicament, such as a vasoconstrictive amine or its acid-addition salts, a hormone, enzyme, alkaloid, steroid, analgesic, bronchodilator, antihistamine, antitussive, anginal preparation, antibiotic and sulfonamide and synergistic combinations of these. Examples of the medications which may be employed are: isoproterenol [alpha-(isopropylaminomethyl) protocatechual alcohol] hydrochloride or sulfate, phenylephrine, phenylpropanolamine, glucagon, adrenochrome, trypsin, ephinephrine, ephedrine, narcotine, codeine, atropine, morphine, dihydromorphinone, ergotamine, scopolamine, methapyrilene, cyanocobalamin, and colchicine. Others are antibiotics such as neomycin, streptomycin, penicillin, procaine penicillin, tetracycline, chlortetracycline and hydroxytetracycline; adrenocorticotropic hormone, and adrenocortical hormones, such as cortisone, hydrocortisone, hydrocortisone acetate and prednisolone; and insulin. The active solid component may also be a cosmetic substance such as talc, an antiperspirant such as aluminium chlorohydrate; a polishing material such as jeweler's rouge; a dye, such as the approved food colorings; a lubricant, such as graphite and other finely-divided materials.

The liquefied propellant employed is one which is a gas at room temperature (65°F.) 50 and atmospheric pressure (760 mm. of mercury), i.e., it shall have a boiling point below 65°F. at atmospheric pressure. For use in compositions intended to produce aerosols for medicinal or cosmetic use, the liquefied propellant should be non-toxic. Among the suitable liquefied propellants which may be employed are the lower alkanes containing up to five carbon atoms, such as butane and pentane, or a lower alkyl chloride, such as methyl, ethyl or propyl chlorides. The most suitable liquefied propellants are the fluorinated and fluorochlorinated lower alkanes such as are sold under the Registered Trade Mark 60 "Freon". Mixtures of the above mentioned

propellants may suitably be employed.

It is contemplated that the fluorinated or fluorochlorinated lower alkane shall contain not more than two carbon atoms and at least one fluorine atom. The preferred halogenated lower alkane compounds may be represented generally by the formula $C_mH_nCl_zF_y$, wherein m is an integer less than 3, n is an integer or zero, y is an integer or zero, and z is an integer, such that $n+y+z = 2m+2$. Examples of these propellants are dichlorodifluoromethane ("Freon 12"), dichlorotetrafluoroethane ("Freon 114") CCl_2CF_2 , trichloromonofluoromethane ("Freon 11"), dichloromonofluoromethane ("Freon 21"), monochlorodifluoromethane ("Freon 22"), trichlorotrifluoroethane ("Freon 113"), and monochlorotrifluoromethane ("Freon 13"). Propellants with improved vapor pressure characteristics may be obtained by using certain mixtures of these compounds, e.g., "Freon 11" with "Freon 12", or "Freon 12" with "Freon 114". For example, dichlorodifluoromethane, which has a vapor pressure of about 70 pounds per square inch gauge and 1,2-dichloro-1,1,2,2-tetrafluoro-ethane ("Freon 114"), with a vapor pressure of about 70 pounds per square inch gauge at 70°F., may be mixed in various proportions to form a propellant having an intermediate vapor pressure which is well suited for use in relatively low pressure containers.

It is most desirable that the vapor pressure of the propellant employed shall itself be between 25 and 65 pounds per square inch gauge at 70°F., and preferably between 30 and 40 pounds per square inch gauge at that temperature. A one-component propellant defined for use in the composition was found to give a composition with gauge pressures in the range of 55 to 65 pounds per square inch at 70°F., which are usable safely with metal containers. The two-component propellants, such as equal weight mixtures of "Freon 12" and "Freon 11", were found to give gauge pressures in the range of 20 to 40 pounds per square inch at 70°F., which are usable safely with specially reinforced glass containers.

It is usually desirable to keep the gas pressure as low as possible, within the limits imposed by the desired specific gravity of the propellant, in order to enable simple containers to be used safely and to prevent too high a pressure causing too wide a dispersal of the powder aerosol. When stronger containers, for example of stainless steel, can be used and the active solid medicament is intended for pulmonary ingestion, it is advantageous to use a propellant with a gauge pressure of between 40 and 50 pounds per square inch;

this allows complete aerosolization before the stream reaches the back of the throat. Since the powder is already present in the composition dispersed in the desired particle size, there is no need for further breakup action in the valve or applicator, so valves of simple construction may be used, and there is no need to provide special nozzles and expansion chambers, as is usually required when dispensing materials which are dissolved in the propellant, or in a liquid which is emulsified with the propellant.

While we do not wish to be bound by any theory to explain the excellent results which are obtained with the compositions of the invention, evidence available to date indicates that the surface-active agent acts by forming a surface coating, which may even be a mono-molecular film or layer, on the finely-divided powder which prevents the particles from agglomerating either while dispersed in the propellant or when in the valve of the container.

After an extensive investigation employing many surface-active agents, we have discovered that particular agents or combinations of them are required to give desirable results. During this investigation it was found unexpectedly that a number of surface-active agents provided poor suspensions and failed to prevent agglomeration.

The liquid, non-ionic, surface-active agent employed should have an hydrophile-lipophile balance (HLB) ratio of less than 10. The HLB ratio is an empirical number which provides a guide to the surface-active properties of a surface-active agent. The lower the HLB ratio, the more lipophilic is the agent, and conversely, the higher the HLB ratio, the more hydrophilic is the agent. The HLB ratio is well known and understood by the colloid chemist and its method of determination is described by W. C. Griffin in the *Journal of the Society of Cosmetic Chemists*, Vol. 1, No. 5, pages 311-326 (1949). Preferably the surface-active agent employed should have an HLB ratio of 1 to 5. It is possible to employ surface-active agents which themselves do not possess an HLB ratio within these ranges providing they are used in conjunction with other surface-active agents which have an HLB ratio which will provide a mixture having an HLB ratio within the prescribed range.

Surface-active agents which are solids at room temperature have been tried but

appear to be unacceptable generally due to clogging of the valve and adapter orifices on delivery. Lubricants for the valve, such as calcium stearate, which is without surfactant properties, were not found to be satisfactory, because they do not help to keep the powdered medicament uniformly dispersed in the propellant.

Those surface-active agents which are soluble or dispersible in the propellant are effective. The more propellant-soluble surface-active agents are the most effective.

For medicinal use it is also important that the surface-active agent should be non-irritating and non-toxic.

We have found that among the liquid non-ionic surface-active agents which may be employed in our compositions are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octoic, lauric, palmitic, stearic, linoleic, linolenic, eleostearic and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride such as, for example, ethylene glycol, glycerol, erythritol, arabitol, mannitol, sorbitol, the hexitol anhydrides derived from sorbitol (the sorbitan esters sold under the Registered Trade Mark "Spans") and the polyoxyethylene and polyoxypropylene derivatives of these esters. Mixed esters, such as mixed or natural glycerides, i.e., olive oil, may be employed. The preferred surface-active agents are the oleates of sorbitan, e.g., those sold under the Registered Trade Marks "Arlacel C" (Sorbitan sesquioleate), "Span 80" (Sorbitan monooleate) and "Span 85" (Sorbitan trioleate).

Specific examples of other surface-active agents which may be employed are:

sorbitan monolaurate
polyoxyethylene sorbitol tetraoleate
polyoxyethylene sorbitol pentaoleate
polyoxypropylene mannitol dioleate

Indicative of the specificity of the surface-active agent in the compositions of the invention, there is reported below the results obtained with surface-active agents falling outside of the scope of the present invention and certain lubricants. These results are based upon tests employing the surface-active agent or lubricant in a concentration of 0.5% with a suspension of 0.5% of hydrocortisone acetate in a "Freon" mixture consisting of 30% "Freon 11" and 70% of a mixture ("Freon W") containing 61.5% "Freon 114" and 38.5% "Freon 12". Hydrocortisone acetate was used because it is one of the more easily suspended materials.

Compound Tested

Paraffin Wax

120

Stearic Acid

Results

Deposits as a solid in the adapter leading from the discharge valve and impairs delivery. Non-homogeneous suspension. Lubricates valve.

Same as for paraffin wax.

	Stearyl Alcohol (solid)	Same as for paraffin wax.
5	Beeswax	Same as for paraffin wax.
	Petrolatum	Petrolatum suspends in "Freon." Fair emulsion, but separates rapidly. Sticks to sides of container. Lubricates valve. Unsafe for inhalation therapy.
10	Oleyl Alcohol (liquid)	Poor suspension, not very homogeneous. Separates quite rapidly. Lubricates valve.
15	Polyethylene Glycol 300	Immiscible with "Freon."
	Mineral Oil	Poor suspension, clumpy, breaks rapidly. Lubricates valve. Unsafe for inhalation therapy.
20	Isopropyl myristate	Fair suspension, but not suitably homogeneous. Causes sticking of discharge valve.
	"MYRJ 45"** (Polyoxethylene stearate)	Very good suspension, clumpy, sticks to container, breaks very rapidly. Lubricates valve.
25	"Brij 30" (Polyoxyethylene lauryl alcohol)	Very poor suspension, clumpy, lubricates valve.
	"Tween 81"** (Polyoxyethylene sorbitan mono-oleate)	Very poor suspension, clumpy. Lubricates valve.

* "MYRJ" and "Tween" are registered Trade Marks.

We have further discovered that in the case of compositions of the invention employing certain finely-divided powders there is a tendency to form a layer of powder at the surface of the propellant in the container and that these layers tend to deposit or "cake" powdered material on the container walls above the liquid level. This has been found to occur only with those powders which have a specific gravity less than that of the propellant.

This tendency to deposit or "cake out" is a serious disadvantage in that (1) such powder deposited on the container walls is not dispensed from the container, (2) the dose delivered is not correct and becomes progressively less as the amount left in the container becomes smaller and (3) in a transparent container the appearance of the product is impaired. The greater the difference in specific gravity between the powder and the propellant, the more pronounced in this tendency. By means of the present invention, it is possible to overcome these drawbacks and to provide more stable, uniform, attractive and satisfactory aerosol-producing compositions.

60 In some cases the undesirable deposition or caking which results where the specific gravity of the finely divided powder is substantially less than that of the propellant can be overcome by lowering the specific

gravity of the liquid phase, for example by using a propellant of lower specific gravity, such as butane, or by increasing the specific gravity of the solid active powder component, for example in the case of phenylephrine by using the bitartrate salt instead of the hydrochloride. In many cases, however, it is not possible to find a suitable alternative form of the active material. In such cases we have discovered, surprisingly, that the introduction of a sufficient quantity of an additional auxiliary finely divided solid of density greater than that of the liquid phase, will prevent the surface spread of lighter powders, thus avoiding "caking out" and the associated, above-mentioned drawbacks.

The nature of such an auxiliary solid may be of any chemical type, provided that it is compatible with the other ingredients and insoluble in the propellant. For example, we may use an inorganic compound such as sodium sulfate, calcium chloride or sodium chloride. We may also use an organic material such as powdered lactose, sucrose, epinephrine bitartrate, neomycin sulfate, or graphite. The auxiliary solid, when used in medicinal and cosmetic preparations, should be non-toxic and non-irritant. In all cases it should be without deleterious effect on the properties of the dispensed product or on the user. The

particle size of the auxiliary solid should be of the same order of magnitude as the active ingredients. The auxiliary powder may also function as a desiccant for the self-propelling compositions as in the case of anhydrous sodium sulfate or calcium chloride or a clinically active component in the case of a medicinal preparation. Such clinically active component is illus-

trated by neomycin sulfate and epinephrine 10 bitartrate.

We have discovered that the quantity of the auxiliary powder which is employed shall desirably fall within certain limits. This amount will be discussed below. 15

If the following symbols have the meaning given:

$$\rho_A = \text{sp. gr. of auxiliary solid}$$

$$\rho_P = \text{sp. gr. of propellant}$$

$$20 \quad \rho_Q = \text{sp. gr. of total powder constituents (auxiliary solid and active constituent)}$$

$$\rho_U = \text{sp. gr. of active constituent}$$

$$a = \text{wt. of auxiliary solids}$$

$$\rho = \text{wt. of propellant}$$

$$q = \text{wt. of total powder constituents}$$

20

$$u = \text{wt. of active constituent}$$

It is apparent that $q = u + a$ (1)

25 To prevent surface deposit or caking the following condition must exist:

ρ_Q minus ρ_P must not be less than zero (2)
This condition is satisfied when: q equals u ,
a equals zero and ρ_U is equal to or greater
30 than ρ_P (3)

But when ρ_U is less than ρ_P , the following exists:

$$35 \quad \rho_Q = \frac{u+a}{\frac{u}{\rho_U} + \frac{a}{\rho_A}}$$

40 or

$$\rho_Q = \frac{(u+a)\rho_U\rho_A}{u\rho_A + a\rho_U} \quad (4)$$

45

For a theoretical minimum, condition (2) becomes:

$$50 \quad \rho_Q \text{ minus } \rho_P = \text{zero or } \rho_Q = \rho_P$$

Applying this information to equation (4),
55 then:

$$60 \quad \frac{(u+a)\rho_U\rho_A}{u\rho_A + a\rho_U} = \rho_P$$

thus:

$$65 \quad a_{\min.} = \frac{u\rho_A(\rho_P - \rho_U)}{\rho_U(\rho_A - \rho_P)} \quad (5)$$

In terms of the above defined symbols, when ρ_U is equal to or greater than ρ_P , a satisfactory composition is obtained whereby no surface deposit or caking of powder is

obtained without the employment of an auxiliary solid or powder. When ρ_U is less than ρ_P , the minimum amount of auxiliary solid required to prevent deposit of solid from the composition, is expressed by equation (5) above. We have found that satisfactory results may be obtained when up to about ten times the minimum is employed, but we prefer to employ between $a_{\min.}$ and three times $a_{\min.}$

The compositions of the invention may be used to apply measured amounts of aerosolized solid medicaments into body cavities such as the throat or nose. They also provide a means of producing aerosolized medicaments suitable for inhalation therapy. Inhalation therapy is prompt through the intimate contact with the blood through the alveolar membrane. It also enables drugs to act directly on respiratory sites without engendering undesirable systemic effects as happens often when drugs are administered by other routes. With very volatile substances inhalation approaches intravenous therapy in rapidity of action. It will often avoid the necessity of parenteral injections. Previously aerosols for this purpose have been prepared by nebulizing aqueous solutions, for example penicillin solutions in the treatment of pneumonia. Suspensions in oil have been suggested in the treatment of bronchial asthma, but this is now widely condemned by the medical profession.

In producing the compositions and packages of the invention, a container equipped with a valve is filled with a propellant containing the finely-divided powder in suspension. A container may first be charged with a weighed amount of dry powder which has been ground to a predetermined particle size, or with a slurry of powder in the cooled liquid propellant. Alternatively and preferably, the powder and the surface-active agent may be triturated or homogenized first into a uniform paste, for instance, by a pestle and mortar. This paste is then dispersed in the cooled liquefied propellant. This procedure fosters uniform wetting of the powder

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particles. A container may also be filled by introducing powder and propellant by the normal cold filling method, or a slurry of the powder in that component of the propellant which boils above room temperature may be placed in the container, the valve sealed in place, and the balance of the propellant may be introduced by pressure filling through the valve nozzle. On operating the valve, the powder will be dispensed in a stream of propellant, which will vaporize providing an aerosol of dry powder. Throughout the preparation of the product care is desirably exercised to minimize the absorption of moisture where the powder is water-soluble. This may be accomplished by operating in a dehumidified atmosphere using only dry materials and equipment.

When it is necessary to employ an auxiliary solid or powder to prevent surface deposit or caking, it is desirably introduced into the composition at the time that powdered active solids are introduced. This process has been employed in Examples 20 to 30 below. Alternatively, the auxiliary solid can be added to the composition after pre-wetting it with the surface-active agent

or propellant

In order more clearly to disclose the nature of the present invention, the following examples illustrating compositions in accordance with the invention will now be described. It should be understood, however, that this is done solely by way of example and is intended neither to delineate the scope of the invention nor limit the ambit of the appended claims. In the examples which follow, the process described above was employed. In the examples which follow and throughout the specification, the quantities of material are expressed in terms of percentages by weight of the total composition, unless otherwise specified. The range of particle size specified in each example is that existing at the time of formulation. Where a constituent is described as "micronized", it comprises 90% by weight of particles having a particle size range of between 1 and 5 microns. Examples 20 through 30 illustrate compositions in accordance with the invention employing an auxiliary solid to prevent surface deposit or caking.

EXAMPLE 1

55	Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns)	3.0%	55
"	" Span 85" (Sorbitan trioleate)	1.0	
"	" Freon 11" (Trichloromonofluoromethane)	30.0	
"	" Freon 114" (Dichlorotetrafluoroethane)	41.0	
60	" Freon 12" (Dichlorodifluoromethane)	25.0	60

EXAMPLE 2

Trypsin, amorphous (more than 90% by weight within the particle size range of 1 to 10 microns)	100.0%	
65 " Span 85" (Sorbitan trioleate)	0.10 gm.	
Propellant A	0.05 gm.	65
(Propellant A consists of: Butane 2.0% and " Freon W" 98.0%. " Freon W" consists of: " Freon 114" (Dichlorotetrafluoroethane) 61.5% and " Freon 12" (Dichlorodifluoromethane) 38.5%).						10.00 gm.	

EXAMPLE 3

70 Prednisolone acetate, crystalline (More than 90% by weight within the particle size range of 1 to 5 microns)	0.5%	70
" Span 85" (Sorbitan trioleate)	0.5	
" Propellant B"	99.0	
75							100.0%

" Propellant B" consists of:							
" Freon 11" (Trichloromonofluoromethane)	10.0%	
" Freon 114" (Dichlorotetrafluoroethane)	50.4	
80 " Freon 12" (Dichlorodifluoromethane)	31.6	80
Butane	8.0	
							100.0%

EXAMPLE 4

85 ACTH (Adrenocorticotropic) (amorphous) (10 USP units/mg.) (more than 90% by weight within the particle size range of 1 to 20 microns)	1.00%	85
" Span 85" (Sorbitan trioleate)	0.25	
" Freon 11" (Trichloromonofluoromethane)	5.00	
" Freon W" (as defined in Example 2)	93.75	
90				100.00%

EXAMPLE 5

ACTH (Adrenocorticotropin) (amorphous) (10 USP units/mg.) (more than 90% by weight within the particle size range of 1 to 20 microns)	0.25%	
" Span 85 " (Sorbitan trioleate)	0.25	
5 " Freon W " (as defined in Example 2)	99.50	5
	<hr/>	
	100.00%	

EXAMPLE 6

Insulin, amorphous (more than 90% by weight within the particle size range of 1 to 5 microns)	0.25%	10
" Span 85 " (Sorbitan trioleate)	0.25	
" Freon W " (as defined in Example 2)	99.50	
	<hr/>	
	100.00%	

EXAMPLE 7

Epinephrine, crystalline (free base) (more than 90% by weight within the particle size range of 1 to 5 microns)	0.28%	15
" Span 85 " (Sorbitan trioleate)	0.25	
" Freon 11 " (Trichloromonofluoromethane)	5.00	
20 " Freon W " (as defined in Example 2)	94.47	20
	<hr/>	
	100.00%	

EXAMPLE 8

Epinephrine bitartrate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns)	0.50%	25
" Span 85 " (Sorbitan trioleate)	0.50	
" Freon 11 " (Trichloromonofluoromethane)	49.50	
" Freon 12 " (Dichlorodifluoromethane)	49.50	
	<hr/>	
	100.00%	30

EXAMPLE 9

Isopropylarterenol hydrochloride, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns)	0.25%	
" Span 85 " (Sorbitan trioleate)	0.25	
35 " Freon 11 " (Trichloromonofluoromethane)	49.75	35
" Freon 12 " (Dichlorodifluoromethane)	49.75	
	<hr/>	
	100.00%	

EXAMPLE 10

40 Phenylephrine hydrochloride, crystalline (more than 90% by weight within the particle size range of 1 to 25 microns)	0.25%	40
Neomycin sulfate	0.11	
Hydrocortisone	0.04	
" Span 85 " (Sorbitan trioleate)	0.25	
45 " Freon 11 " (Trichloromonofluoromethane)	49.675	45
" Freon 12 " (Dichlorodifluoromethane)	49.675	
	<hr/>	
	100.00%	

EXAMPLE 11

50 Neomycin sulfate, crystalline (more than 90% by weight within the particle size range of 1 to 25 microns)	0.50%	50
" Span 85 " (Sorbitan trioleate)	0.25	
" Freon 11 " (Trichloromonofluoromethane)	4.75	
" Freon W " (as defined by Example 2)	94.50	
	<hr/>	
	100.00%	55

EXAMPLE 12

Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns)	0.50%	
60 " Surfactant G-1087 " (polyoxyethylene sorbitol hexaoleate)	0.50	60
" Propellant C "	99.00	
	<hr/>	
	100.00%	65

(Propellant C consists of: " Freon 11 " (trichloromonofluoromethane) 30.00% and " Freon W " (as defined in Example 2) 70.00%)

EXAMPLE 13

5	Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns)	0.50%
	" Arlacel C " (Sorbitan sesquioleate)	0.50
	5 " Propellant C " (as defined by Example 12)	99.00
			<hr/>
			100.00%

EXAMPLE 14

10	Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns)	0.50%	10
	" Span 80 " (Sorbitan monoleate)	0.50	
	" Propellant C " (as defined by Example 12)	99.00	
			<hr/>	
			100.00%	

EXAMPLE 15

15	Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns)	0.50%	15
	" Span 85 " (Sorbitan trioleate)	0.50	
	" Propellant C " (as defined by Example 12)	99.00	
			<hr/>	
			100.00%	

EXAMPLE 16

20	Narcotine, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns)	10.00%	20
	" Span 85 " (Sorbitan trioleate)	1.00	
	" Freon W " (as defined by Example 2)	89.00	
			<hr/>	
			100.00%	

EXAMPLE 17

25	80 " Dilauidid,"* crystalline (dihydromorphinone hydrochloride) (More than 90% by weight within the particle size range of 1 to 5 microns)	0.5%	25
	" Span 85 " (Sorbitan trioleate)	1.0	
	" Freon 11 " (Trichloromonofluoromethane)	30.0	
	" Freon W " (as defined by Example 2)	68.5	
			<hr/>	
			100.0%	

*The word " Dilauidid " is a registered Trade Mark.

EXAMPLE 18

40	40 Iron oxide (jeweller's rouge) (more than 90% by weight within the particle size range of 1 to 20 microns)	1.0%	40
	" Span 80 " (Sorbitan monooleate)	0.25	
	" Freon 12 " (Dichlorodifluoromethane)	98.75	
			<hr/>	
			100.00%	

45 This composition is useful for polishing optical components.

EXAMPLE 19

50	Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns)	0.5%	50
	Olive Oil	0.5	
	" Freon 11 "	30.0	
	" Freon W " (as defined by Example 2)	69.0	
			<hr/>	
			100.0%	

55	Phenylephrine hydrochloride (crystalline) micronized	0.25%	55
	Phenylpropanolamine hydrochloride (crystalline) micronized	0.50	
	Neomycin sulfate (crystalline) micronized	0.10	
60	60 Hydrocortisone (crystalline) micronized	0.04	60
	Sodium sulfate (anhydrous) micronized	0.35	
	" Span 85 " (Sorbitan trioleate)	0.80	
	Propellant S	97.96	
			<hr/>	

65 100.00% 65

Propellant S consists of:—

“ Freon 12 ”	(Dichlorodifluoromethane)	27%
“ Freon 11 ”	(Trichloromonofluoromethane)	30%
“ Freon 114 ”	(Dichlorotetrafluoroethane)	43%

EXAMPLE 21

5	Phenylephrine hydrochloride (crystalline) micronized	0.25%	5
	Neomycin sulfate (crystalline) micronized	0.10	
	Hydrocortisone (crystalline) micronized	0.04	
	Calcium chloride micronized	0.10	
10	“ Span 85 ” (Sorbitan trioleate)	0.50	10
	Propellant S (as defined by Example 20)	99.01	
						100.00%	

EXAMPLE 22

15	Phenylephrine hydrochloride (crystalline) micronized	0.25%	15
	Sodium chloride (crystalline) powdered	0.50	
	“ Span 85 ” (Sorbitan trioleate)	0.75	
	Propellant S (as defined in Example 20)	98.5	

20						100.00%	20
						0.25%	
	Phenylephrine hydrochloride (crystalline) micronized	0.75	
	Epinephrine bitartrate (crystalline) micronized	1.0	
	“ Span 85 ” (Sorbitan trioleate)	98.0	25
	Propellant S (as defined in Example 20)		
						100.00%	

EXAMPLE 23

25	Phenylephrine hydrochloride (crystalline) micronized	0.25%	
	Sucrose (crystalline) powdered	0.50	30
	“ Span 85 ” (Sorbitan trioleate)	0.75	
	Propellant S (as defined by Example 20)	98.5	

EXAMPLE 24

30	Phenylephrine hydrochloride (crystalline) micronized	0.25%	
	Sucrose (crystalline) powdered	0.50	30
	“ Span 85 ” (Sorbitan trioleate)	0.75	
	Propellant S (as defined by Example 20)	98.5	

EXAMPLE 25

35	Phenylephrine hydrochloride (crystalline) micronized	1.0%	
	Neomycin sulfate (crystalline) micronized	3.0	
	“ Span 85 ” (Sorbitan trioleate)	1.0	
	Propellant S (as defined by Example 20)	95.0	

40						100.00%	40
						0.25%	
	Phenylephrine hydrochloride (crystalline) micronized	0.25	
	Graphite powder	0.50	45
	“ Span 85 ” (Sorbitan trioleate)	99.0	
	Propellant S (as defined by Example 20)		
						100.00%	

EXAMPLE 26

45	Phenylephrine hydrochloride (crystalline) micronized	0.25%	
	Graphite powder	0.25	
	“ Span 85 ” (Sorbitan trioleate)	0.50	45
	Propellant S (as defined by Example 20)		

EXAMPLE 27

50	Hydrocortisone acetate (crystalline) micronized	0.88%	
	Sodium sulfate (anhydrous) micronized	0.88	
	“ Span 85 ” (Sorbitan trioleate)	1.00	
	Propellant S-2	97.24	

55						100.00%	55
						50%	
	Propellant S-2 consists of:						
	“ Freon 12 ” (Dichlorodifluoromethane)	50%	

60	“ Freon 12 ” (Dichlorodifluoromethane)	50%	
	“ Freon 11 ” (Trichloromonofluoromethane)	25%	
	“ Freon 114 ” (Dichlorotetrafluoroethane)	25%	

EXAMPLE 28

60	Phenylephrine hydrochloride (crystalline) micronized	0.25%	
	Lactose, powdered	0.50	
	“ Span 85 ” (Sorbitan trioleate)	0.75	
	Propellant S (as defined by Example 20)	98.5	

65						100.00%	65

EXAMPLE 29

5	Phenylephrine hydrochloride (crystalline) micronized	0.25%
	Neomycin sulfate (crystalline) micronized	0.08
	" Span 85 " (Sorbitan trioleate)	0.50
	5 Sodium sulfate, micronized	0.10
	Propellant X	99.07
					100.00%

Propellant X consists of:

10	" Freon 12 " (Dichlorodifluoromethane)	30%
	" Freon 11 " (Trichloromonofluoromethane)	30%
	" Freon 114 " (Dichlorotetrafluoroethane)	40%

15

15					15

EXAMPLE 30

20	Phenylephrine hydrochloride (crystalline) micronized	0.25%
	Neomycin sulfate (crystalline) micronized	0.08%
	Thenylpyramine hydrochloride (crystalline) micronized	0.20
	20 Sodium sulfate (crystalline) micronized	0.15
	" Span 85 " (Sorbitan trioleate)	0.70
	Propellant X (as defined by Example 29)	98.62
					100.00%

25					25

EXAMPLE 31

30	Isoproterenol sulfate, (crystalline), micronized	0.15%
	" Span 85 " (Sorbitan trioleate)	0.50
	" Freon 113 " (Trichlorotrifluoroethane)	0.95
	" Freon 11 " (Trichloromonofluoromethane)	24.60
	30 " Freon 114 " (Dichlorotetrafluoroethane)	24.60
	" Freon 12 " (Dichlorodifluoromethane)	49.20
					100.00%

35					35

EXAMPLE 32

40	35 Phenylpropanolamine hydrochloride, (crystalline) micronized	0.49%
	Phenylephrine hydrochloride, (crystalline) micronized	0.25
	Neomycin sulfate, (crystalline) micronized	0.10
	Hydrocortisone, (crystalline) micronized	0.04
	Sodium sulfate, (crystalline) (anhydrous) micronized	0.35
	40 " Span 85 "	1.00
	" Freon 113 "	1.00
	" Freon 11 "	29.03
	" Freon 12 "	29.03
	" Freon 114 "	38.71
					100.00%

45					45

EXAMPLE 33

50	Phenylephrine hydrochloride, (crystalline) micronized	0.25%
	Phenylpropanolamine hydrochloride, (crystalline) micronized	0.50
	50 Neomycin sulfate, (crystalline), micronized	0.08
	Methapyrilene hydrochloride, (crystalline) micronized	0.10
	Sodium sulfate, (crystalline) micronized	0.35
	" Span 85 "	1.00
	" Freon 113 "	1.00
	55 " Freon 11 "	29.01
	" Freon 114 "	38.70
	" Freon 12 "	29.01
					100.00%

60					60

EXAMPLE 34

65	Crystalline glucagon, micronized	0.156%
	" Span 85 "	0.468
	" Propellant S " (as defined by Example 20)	99.376

100.000% 65

		EXAMPLE 35	
	Anhydrous cyanocobalamin, (crystalline) micronized	0.039%
	" Span 85 "	0.250
	" Propellant S " (as defined by Example 20)	99.711
5			<hr/> 100.000% 5
		EXAMPLE 36	
	Chlortetracycline hydrochloride, (crystalline) micronized	0.5%
	Lactose	0.5
10	" Span 85 "	1.0
	" Propellant S " (as defined by Example 20)	98.0
			<hr/> 100.0% 10
		EXAMPLE 37	
15	Adrenochrome, (crystalline) micronized	1.785% 15
	" Span 85 "	1.0
	" Propellant S " (as defined by Example 20)	97.215
			<hr/> 100.000% 20
		EXAMPLE 38	
20	Phenylephrine hydrochloride, (crystalline) micronized	0.253%
	Neomycin sulfate, (crystalline) micronized	0.080
	Methapyrilene hydrochloride, (crystalline) micronized	0.198
	Anhydrous sodium sulfate, (crystalline) micronized	0.150
25	" Span 85 "	1.00
	" Propellant X " (as defined by Example 29)	98.319
			<hr/> 100.000% 25

30 WHAT WE CLAIM IS :—

1. A self-propelling composition capable of dispensing a powder in aerosol form and comprising a finely divided powder suspended in a mixture of a liquefied propellant having a boiling point below 65°F. at atmospheric pressure and a liquid, non-ionic surface-active agent.
2. A composition according to Claim 1, in which the powder has a substantially uniform particle size of less than 25 microns.
3. A composition according to Claim 1 or 2, in which the surface-active agent is soluble in the propellant.
4. A composition according to any one of Claims 1-3, in which the powder is substantially insoluble in the mixture of propellant and surface-active agent.
5. A composition according to any one of Claims 1-4, in which the surface-active agent has a hydrophile-lipophile balance ratio of less than 10, preferably between 1 and 5.
6. A composition according to any one of Claims 1-5, in which the powder constitutes between 0.01% and 20% by weight and the surface-active agent between 0.1% and 20% by weight of the total composition.
7. A composition according to any one of Claims 1-6, in which the moisture content is kept below 300 parts per million by weight of the total composition.
8. A composition according to any one of Claims 1-7, in which the surface-active agent is an ester of a polyhydroxy compound.
9. A composition according to any one of Claims 1-8, in which the surface-active agent

is a fatty acid ester of sorbitan, preferably an unsaturated fatty acid ester of sorbitan such as an oleic acid ester of sorbitan.

10. A composition according to any one of Claims 1-9, in which the powder is prednisolone or one of its esters.

11. A composition according to any one of Claims 1-9, in which the powder is epinephrine or one of its salts.

12. A composition according to any one of Claims 1-9, in which the powder is a salt of isoproterenol such as isoproterenol sulfate or isoproterenol hydrochloride.

13. A composition according to any one of Claims 1-9, in which the powder comprises a mixture of phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and methapyrilene hydrochloride.

14. A composition according to any one of Claims 1-9, in which the powder comprises a mixture of phenylpropanolamine hydrochloride, phenylephrine hydrochloride, neomycin sulfate and hydrocortisone.

15. A composition according to any one of Claims 1-9, in which the powder is glucagon.

16. A composition according to any one of Claims 1-9, in which the powder is cyanocobalamin.

17. A composition according to any one of Claims 1-9, in which the powder is chlortetracycline hydrochloride.

18. A composition according to any one of Claims 1-9, in which the powder is adrenochrome.

19. A composition according to any one of Claims 1-18, in which the specific gravity of

the powder is at least as great as that of the liquefied propellant.

20. A composition according to any one of Claims 1-19, in which the powder comprises "u" units by weight of a useful substance of specific gravity " ρ_u ", the powder including "a" units by weight of an auxiliary solid substance of specific gravity " ρ_A " the propellant having a specific gravity " ρ_P " and the minimum value of "a" being expressed as follows:

$$15 \quad a_{\min.} = \frac{u \cdot \rho_A (\rho_P - \rho_u)}{\rho_u (\rho_A - \rho_P)}$$

21. A composition according to Claim 20, in which "a" lies between the value of " $a_{\min.}$ " and 10 times " $a_{\min.}$ ". preferably 20 between the value of " $a_{\min.}$ " and 3 times

" $a_{\min.}$ ".

22. A composition according to Claim 20 or 21, in which the auxiliary solid is sodium sulfate or calcium chloride.

23. A composition according to Claim 20 or 21, in which the auxiliary solid is lactose or sucrose.

24. A self-propelling composition capable of dispensing a powder in aerosol form substantially as hereinbefore described in the accompanying examples.

25. A package comprising a pressure-tight container having a valve-controlled opening and containing a self-propelling composition according to any one of Claims 1-24. 35

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Printed for Her Majesty's Stationery Office by Wickes & Andrews, Ltd., E.C.4. 684/2.—1960.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies
may be obtained.